
SUMMARY

A brief overview of the incidence, etiology and current controversies in the management of penile cancer is provided in **chapter 1**. In **chapter 2**, the prognostic and practical value of the current TNM classification for penile carcinoma is evaluated in 513 patients treated at The Netherlands Cancer Institute (NKI). The disease-specific survival was calculated using Kaplan Meier and log rank analysis for all T- and N-categories. No significant difference in survival was found between the current T2 and T3 tumours ($p=0.57$). Furthermore, there was no significant survival difference between the N1 and N2-categories ($p=0.18$). Using a modified classification, a significant difference in survival was found between all T and N-categories. Furthermore, clinical staging is facilitated.

Penile cancer has a lymphogenic dissemination pattern. In **chapter 3**, an overview of the current management of the regional lymph nodes is provided. The first draining lymph nodes are in the inguinal region. Around 20% of clinically node-negative (cN0) patients have occult inguinal metastasis and there is evidence that these patients benefit from early dissection compared to removal at the time the occult metastases become clinically apparent. In most centres, an elective lymph node dissection is standard of care in cN0 patients, although this procedure is associated with substantial morbidity. Alternative techniques to select the patients with occult metastasis are risk prediction based on primary tumour characteristics, imaging techniques such as ultrasound or magnetic resonance imaging (MRI) and dynamic sentinel node biopsy (DSNB). It is concluded that surgical staging is currently the only reliable method to identify the patients with occult metastases. DSNB is a minimally invasive option with a high sensitivity and low morbidity.

In **chapter 4**, the value of gene-expression profiling as a predictor of the tumour-status of the regional nodes in patients with penile carcinoma is evaluated. Tumour samples of 56 patients were analysed for gene-expression using 35K oligoarrays. In a training-set of 30 tumour samples, a 44-probe classifier was found to have the best performance for the prediction of nodal metastasis. In the validation set of 26 samples, a disappointing accuracy of 54% was found. The sensitivity and specificity of the 44-probe classifier was 71% and 22%, respectively. Microarray gene-expression profiling did not produce a useful classifier to predict nodal involvement in patients with penile carcinoma.

In **chapter 5**, the value of hybrid ^{18}F -FDG positron emission tomography / computed tomography (PET/CT) for the prediction of occult metastasis is evaluated. In 24 patients with 42 cN0 groins scheduled to undergo DSNB, a preoperative hybrid PET/CT scan was performed to assess the nodal status of the cN0 groins. The histopathological tumour-status of the removed sentinel node was used as the gold standard to evaluate the PET/CT results. One of the five tumour-positive cN0 groins was correctly predicted on the PET/CT images (sensitivity 20%). All false-negative

PET/CT scans contained metastases ≤ 10 mm. Of the remaining 37 tumour-negative groins, 34 were correctly predicted with PET/CT (specificity 92%). It is concluded, that the role of PET/CT in the evaluation of the groins in cN0 penile cancer patients is limited due to its low sensitivity.

In **chapter 6**, the lymphatic drainage pattern of 50 cN0 penile cancer patients scheduled to undergo DSNB was analysed using a hybrid single photon emission computed tomography/CT (SPECT/CT) scanner. The groin was divided according to the five Daseler's zones: four zones by drawing a vertical and horizontal line over the saphenofemoral junction, and one zone directly overlying this junction. The visualised sentinel-nodes and higher-tier nodes were divided into these zones. All sentinel nodes were found in the superior and central inguinal zones and no lymphatic drainage was seen to the inferior two regions of the groin. This suggests that the extent of an inguinal node dissection in cN0 patients could be reduced to removal of the superior and central inguinal zones. This may decrease the extensive morbidity associated with this procedure.

In **chapter 7**, the current results from DSNB at NKI were evaluated. Over time, several modifications such as preoperative ultrasound and improved histopathological analysis were made to reduce the false-negative rate of DSNB. The false-negative and complication rate of the current procedure, as performed at NKI since 2001, were compared with results from the prior procedures. Since the modifications, the false-negative dropped from 19.2% to 4.8%. The complication rate decreased from 10.2% to 5.7%. DSNB has matured into a reliable and safe method for assessing lymph node status in cN0 penile carcinoma patients. Despite the encouraging results from DSNB at NKI, in most centres an elective inguinal lymph node dissection is still standard of care. Reservations to the introduction of DSNB include the fact that most results come from one institution and the supposedly long learning curve associated with the procedure. In **chapter 8**, these issues are addressed by evaluating DSNB results from two centres: NKI and St. George's Hospital in London (SGH). DSNB was introduced in 2004 at SGH based on the current protocol from NKI. The presence of a learning curve at SGH was evaluated. The combined false-negative rate was 7% (6.7% at NKI and 7.5% at SGH). Complications occurred in 4.7% of explored groins (5.7% at NKI and 3.5% at SGH). None of the false-negative cases occurred in the initial 30 procedures at SGH. It is concluded that sentinel node biopsy is a suitable procedure to stage cN0 penile cancer with a low complication rate. The satisfactory results from NKI can also be achieved by a centre newly introducing the technique according to a structured protocol. No learning curve was demonstrated in this study.

One of the suggested causes of a false-negative sentinel node procedure is extensive metastatic involvement of a sentinel node that leads to blocked inflow and rerouting of lymph fluid to a 'neo'-sentinel node that may not yet contain tumour. There is, however, little evidence to support this hypothesis. In **chapter 9**, hybrid SPECT/

CT was used to evaluate the concept of tumour-blockage and rerouting in penile carcinoma patients with palpable groin metastases. The pattern of lymphatic drainage in the 17 palpable and cytologically confirmed metastatic groins was evaluated for signs of tumour-blockage or rerouting. Four of the 17 palpable metastatic nodes (24%) showed uptake of radioactivity on the SPECT/CT images. In 10 groins, rerouting of lymphatic drainage to a neo-sentinel node was seen. Complete absence of lymphatic drainage was seen in the three remaining groins. The assumed concept of tumour-blockage and rerouting was visualised in 76% of the groins with palpable metastases. Although these results are based on clinically node-positive groins, they can probably be extrapolated to cN0 groins. Conscientious physical examination and ultrasound with fine-needle aspiration cytology before DSNB may identify impalpable nodes with considerable tumour invasion at an earlier stage and thereby reduce the incidence of false-negative procedures.

Chapter 10 focuses on the role of neo-adjuvant chemotherapy for advanced penile carcinoma. At NKI, 20 patients received neo-adjuvant chemotherapy for downstaging of irresectable disease in the period from 1972 until 2005. The clinical tumour response, chemotherapeutic toxicity, subsequent surgery and long term clinical outcome were evaluated. An objective tumour response was achieved in 12 of 19 evaluable patients. Overall five-year survival was 32%. A significant difference ($p=0.012$) in survival was found between responders (five-year survival 56%) and non-responders (all patients died within nine months). Nine responders underwent subsequent surgery with curative intent. Eight of them were long-term survivors without evidence of recurrent disease. Toxicity of chemotherapy was high with three toxic deaths and discontinuation of treatment in one patient. These results suggest that neo-adjuvant chemotherapy is a valuable treatment option for patients with irresectable penile carcinoma, otherwise considered not curable.

In **chapter 11**, 700 patients from two referral centres for penile carcinoma (NKI and Örebro University Hospital, Sweden) were evaluated for recurrences in order to find a rational follow-up regimen. Recurrences were categorised as local, regional or distant. The rate of local recurrences was compared between patients undergoing penile preserving treatments and partial/total amputation. Regional recurrences were compared between patients surgically staged as node-negative or node-positive and cN0 patients subjected to a wait-and-see policy. A total of 205 out of 700 patients (29.3%) had a recurrence. Of these, 92.2% occurred within five years after primary treatment. The local recurrence rate was 27.7% after penile preserving therapy and 5.3% after amputation. The regional recurrence rate was 2.3% in patients surgically staged as node-negative, 19.1% when surgically staged as node-positive and 9.1% in patients undergoing a wait-and-see policy. It is concluded that patients undergoing penile-preserving therapy, patients surgically staged as node-positive and those undergoing a wait-and-see policy for the nodal status are at high risk of developing a

recurrence. Follow-up recommendations are provided, based on the risk and impact on survival of a recurrence. In **chapter 12**, future prospects in the management of penile cancer are discussed.